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EXAMINER

FLOOD, MICHELE C

ART UNIT

PAPER NUMBER

1654

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/992,860	Applicant(s) Chen et al.
	Examiner Michele Flood	Art Unit 1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on Sep 3, 2002

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-3 and 6-29 is/are pending in the application.

4a) Of the above, claim(s) 1-3, 10, 11, and 16-29 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 6-9 and 12-15 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some* c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)

4) Interview Summary (PTO-413) Paper No(s). _____

2) Notice of Draftsperson's Patent Drawing Review (PTO-946)

5) Notice of Informal Patent Application (PTO-152)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s). 9 & 10

6) Other: _____

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DETAILED ACTION

Election/Restriction

Acknowledgment is made of Applicant's election without traverse of cancer as a species for prosecution on the merits in Paper No. 12 is acknowledged.

Claims 6-17 have been examined, insofar, as they read on the elected invention, namely orange peel extract and cancer. Thus, Claims 10-11 and 16-17 are withdrawn from consideration as claims drawn to an non-elected invention.

Specification

The specification is objected to for the following informality:

There is an apparent typographical error on page 11, line 2, "y". Applicant may overcome the objection by replacing "y" with by.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-9 and 12-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of inhibiting the growth of cancer cells

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comprising administering an effective dose amount of a black tea extract comprising theaflavin-3-gallate and theaflavin-3'-gallate to cancerous cell lines, does not reasonably provide enablement for a method for preventing or treating any all diseases or conditions in an animal by modulating Cox-2 gene expression comprising administering to the animal the claim-designated plant extract. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to a method for preventing or treating a disease or a condition in an animal by modulating Cox-2 gene expression, the method comprising administering to the animal a composition comprising black tea extract which comprises theaflavin-3-gallate and theaflavin-3'-gallate in an amount sufficient to modulate the Cox-2 gene expression wherein the disease or condition is selected from the group consisting of cancer, inflammation and arthritis. The claims are further directed to a method wherein the disease or condition is cancer; wherein the cancer is colorectal cancer; wherein the composition further comprises an orange peel extract; wherein the disease or condition is inflammation; and wherein the disease or condition is arthritis.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2D 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation

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needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

Applicant has demonstrated an *in vitro* method of inhibiting the growth of SV40-transformed W138VA cells, which are cancerous in nude mice, by the administration of TF-2 to the cells at doses in the range of 10 to 50 μ M. Applicant has also demonstrated an *in vitro* method of inhibiting the growth of human Caco-2 colorectal cancer cells by the administration of TF-2 to the cells at doses in the range of 50 or 100 μ M. Applicant concludes on page 4 of the specification, lines 13-15, "These data demonstrate that TF-2 has effects to inhibit cell growth in more than one type of cancer cell." On page 5, lines 5-35 to page 6 in its entirety, Applicant has further demonstrated a method of suppressing enzyme activity of cyclooxygenase-2 activity in Caco-2 cells at doses of 50 to 100 μ M. Thus, while Applicant has demonstrated an *in vitro* method for the inhibition of the growth for two cancerous cell lines, namely virally transformed W138VA cells and Caco-2 human colon cancer cells, comprising the administration of a black tea extract comprising theaflavin-3-gallate and theaflavin-3'-gallate to cancerous cell lines in an amount sufficient to inhibit cancer cell growth, Applicant has not demonstrated a method for preventing or treating any and all diseases or conditions in an animal by modulating Cox-2 gene expression, the method comprising administering to the animal a composition comprising black tea extract which comprises theaflavin-3-gallate and theaflavin-3'-gallate in an amount sufficient to modulate the Cox-2 gene expression, much less a method for the prevention of cancer in an animal by modulating Cox-2 gene expression comprising administering an effective amount of the

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claim-designated plant extract. Moreover, Applicant has not disclosed a method for preventing or treating any and all disease conditions in an animal by modulating Cox-2 gene expression, wherein the composition further comprises an orange peel extract. For example, on page 6 of the application, lines 6-34, Applicant alleges that the effect of TF-2 on Cox-2 gene expression was examined in the aforementioned cancer cells. On page 11 of the specification, lines 15-33, bridging pages 12-14, Applicant discloses assays for DNA fragmentation analysis, Northern Blot analysis, Reverse transcription polymerase chain reaction, and Western Blot analysis, however, nowhere in the specification does Applicant show the data from which Applicant has concluded that the claim designated extract has an effect on modulating Cox-2 gene expression. While it may be possible that the composition, as recited in the claims, could be useful for the claimed functional effect, it seems highly unlikely that the claimed method of treatment, much less the claimed method of prevention, could be used for the treatment or prevention of any and all diseases or conditions in an animal by modulating Cox-2 gene expression given the limited data and experimental models shown by Applicant, even after extensive experimentation.

While the claims do not expressly direct using the claim-designated black tea extract for treating or preventing the growth of cancer cells in humans, the specification does teach delivering the claim-designated plant extract to human cancer cell lines and the functional effect of cell growth inhibition and decrease in the level of Cox-2 protein. Moreover, the specification suggests that the mechanism by which the claim-designated plant extract exerts its anti-tumor effect is the modulation of Cox-2 gene expression. The Office further notes that on page 7, 8, and 9, lines 1-

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29, Applicant discloses the development of nutraceutical dietary supplements comprising the black tea extract of the claimed invention for human consumption. The specification clearly provides a prophetic method for preventing or treating a disease or condition in an animal by modulating Cox-2 gene expression comprising administering to an animal the claimed black tea extract in an amount sufficient to modulate Cox-2 gene expression, wherein the disease or condition is cancer, wherein the cancer is colorectal cancer, and wherein the composition further comprises an orange peel extract. It should be noted that the state of the art at the time of filing suggests that the delivery of therapeutic drugs which exhibit *in vitro* anti-tumor activity do not necessarily have the same beneficial functional effect in humans. For example, Jain (Science, 1996. Vol. 271: 1079-1080) discloses that while promising chemotherapeutic agents exhibit activity against cancer cells *in vitro* and *in vivo* tumor systems, these same agents heralded as breakthrough drugs do not have the same functional effect in humans when delivered to humans bearing tumors. In another example, Dermer (Bio/Technology, 1994. Vol. 12: 320) states, "The cell lines in which cancer is usually studied are unsuitable for the job. They do not mimic conditions in the human body."

Inventions targeted for cancer therapy bear a heavy responsibility to provide supporting evidence because of the unpredictability in biological responses to therapeutic treatments. Moreover, effective treatments for preventing or treating such disease conditions are relatively rare, and may be unbelievable in the absence of supporting evidence. Claims drawn to methods intended for the administration of compounds to cancer cells and/or cancer patients, or in the

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instant case, claims drawn to methods for preventing or treating a disease or condition in an animal by modulating Cox-2 gene expression (which may induce the growth of cancerous cells), generally require supporting evidence because of the unpredictability in biological responses to therapeutic treatments. In order to enable the skilled artisan to practice the invention as claimed, Applicant would have to demonstrate the functional effect and describe the therapeutic effective amounts of the extract intended for a therapeutic or prophylactic treatment for modulating Cox-2 gene expression in any and all diseases or conditions in an animal comprising administering to the animal the claim-designated plant extract in an amount sufficient to modulate Cox-2 gene expression. There is no guidance in the specification, other than the aforementioned examples directed to the delivery of an effective amount of black tea extract which comprises theaflavin-3-gallate and theaflavin-3'-gallate to *in vitro* cancer cell cultures for the reduction of cell number and decrease in the level of Cox-2 protein. Given the insufficient guidance in the specification as to how to carry out the instantly claimed invention for the proposed method of therapeutic treatment, the lack of working examples, and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

The instant invention, as claimed, falls under the “germ of an idea” concept defined by the CAFC. The court has stated that “patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable”. The court continues to say that “tossing out the mere germ of an idea does not constitute an enabling

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disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). The claimed methods of transfer constitute such a "germ of an idea".

According, it would take undue experimentation without a reasonable expectation of success to determine which amounts of the instantly claimed extract would have the claimed functional effect for preventing or treating any and all diseases or conditions in an animal by modulating Cox-2 gene expression, the method comprising administering to the animal a composition comprising black tea extract which comprises theaflavin-3-gallate and theaflavin-3'-gallate in an amount sufficient to modulate the Cox-2 gene expression wherein the disease or condition is cancer, wherein the cancer is colorectal cancer, and wherein the composition further comprises an orange peel, as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6-8 and 12-14 are rejected under rejected under 35 U.S.C. 102(a) as being anticipated by Yang et al. (U).

Applicant claims a method for preventing or treating a disease condition in an animal by modulating Cox-2 gene expression, the method comprising administering to the animal a composition comprising black tea extract which comprises theaflavin-3-gallate and theaflavin-3'-gallate in an amount sufficient to modulate the Cox-2 gene expression wherein the disease or condition is selected from the group consisting of cancer, inflammation and arthritis. Applicant further claims the method of claim 6, wherein the disease or condition is cancer. Applicant further claims the method of claim 7, wherein the cancer is colorectal cancer. Applicant further claims a method for preventing or treating a disease condition in an animal by modulating Cox-2 gene expression, the method comprising administering to the animal a composition comprising theaflavin-3-gallate and theaflavin-3'-gallate in an amount sufficient to modulate the Cox-2 gene expression, wherein the disease or condition is selected from the group consisting of cancer, inflammation and arthritis. Applicant further claims the method of claim 12, wherein the disease or condition is cancer. Applicant further claims the method of claim 13, wherein the cancer is colorectal cancer.

On page 196, lines 7-10, Yang teaches an extract of black tea comprising theaflavin-3-gallate and theaflavin-3'-gallate. On page 194, lines 6-19 bridging page 195, lines 1-12, Yang

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teaches that the administration of an extract of black tea (DBT) inhibits lung tumorigenesis in mice treated with 1-(methylnitrosamino)-1-(3-pyridyl)-butanone (NNK). In a NNK-induced lung tumorigenesis model, Yang further teaches that administering DBT inhibits adenoma formation and cell proliferation (see page 195, line 19 to page 197, lines 1-11). On page 199, lines 27-35, Yang teaches, "Tea inhibits the activity of several enzymes related to tumor promotion and cell proliferation, including ornithine decarboxylase, protein kinase C, cyclooxygenase, and lipoxygenase." Yang does not expressly teach his method of treating cancer comprising the administration to animals an extract of black tea comprising theaflavin-3-gallate and theaflavin-3'-gallate as a method to modulate Cox-2 gene expression. However, as the composition taught by Yang comprises the claimed ingredients obtained from an extract of black tea and the claimed method is a one step method for the administration of the same ingredients having the same and identical functional effect of treating the same disease conditions, the claimed functional effect to modulate Cox-2 gene expression is inherent to the method of administering the composition taught by Yang because cancer is associated with Cox-2 gene expression. Please note that since the prior art procedure teaches the administration of the same ingredients to provide the functional effect of treating the same disease condition as claimed, the prior art procedure inherently must prevent colorectal cancer because the same ingredient is applied in the same way. In re Best 195 USPQ 430, 433 (CCPA 1977). Thus, the prior art procedure reads on preventing colorectal cancer.

The reference anticipates the claimed subject matter.

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Claims 6-8 and 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by DE 19627344 (O).

Applicant's claimed invention of Claims 6-8 and 12-14 was set forth above.

DE 19627344 teaches an extract of *Camellia sinensis* comprising theaflavin-3-gallate and theaflavin-3'-gallate which is used for the prevention or treatment of cancer. DE 19627344 does not expressly teach his method of treating cancer comprising the administration to animals an extract of black tea comprising theaflavin-3-gallate and theaflavin-3'-gallate as a method to modulate Cox-2 gene expression. However, as the composition taught by DE 19627344 comprises the claimed ingredients obtained from an extract of black tea and the claimed method is a one step method for the administration of the same ingredients having the same and identical functional effect of treating the same disease conditions, the claimed functional effect to modulate Cox-2 gene expression is inherent to the method of administering the composition taught by DE 19627344 because cancer is associated with Cox-2 gene expression. Please note that since the prior art procedure teaches the administration of the same ingredients to provide the functional effect of treating the same disease condition as claimed, the prior art procedure inherently must prevent colorectal cancer because the same ingredient is applied in the same way. *In re Best* 195 USPQ 430, 433 (CCPA 1977). Thus, the prior art procedure reads on preventing colorectal cancer.

Therefore, the cited reference is deemed to anticipate the claimed subject matter.

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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 6-9 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang et al. (U) and DE 19627344 (O) in view of Okuda et al. (N) and Xu et al. (V).

Applicant's claimed invention of Claims 6-8 and 12-15 was set forth above. Applicant further claims the method of claim 8 and the method of claim 13, wherein the composition further comprises an orange peel extract

The teachings of Yang and DE 19627344 are set forth above. Yang and DE 19627344 teach the claimed invention except for orange peel extract. However, it would have been obvious to one of ordinary skill in the art to modify the methods of administering the black tea extracts comprising theaflavin-3-gallate and theaflavin-3'-gallate taught by Yang and DE 19627344 by adding orange peel extract to provide the claimed invention because Okuda and Xu teach methods of administering orange peel extract to animals in the treatment of diseases associated with Cox-2 gene expression, such as cancer. Firstly, Okuda teaches a composition comprising an extract of CHINPI (peel of *Citrus aurantium* or orange peel), which inhibited the fat decomposition accelerating action of cancer toxin (toxohormone L) and promoted the lipid

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metabolism and appetite of a patient suffering cancer. Secondly, on page 331, column 2, lines 1-12, Xu teaches that supplementing the diets of human subjects with orange peel powder inhibited the formation of N-nitrosoproline (NRPO). See Figure 3, also. Note that Xu teaches that the NRPO test with L-proline was used as a probe to observe N-nitrosation potential in populations in high-risk areas for gastric cancer. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to modify the methods taught by Yang and DE 19627344 by adding the orange peel extract taught by Okuda and Xu to provide the claimed invention because Yang teaches that orange peel extract has extremely low toxicity and high safety; and, on page 332, column 2, lines 34-45, Xu suggests that orange peel extract contains constituents that can block the carcinogenic process and in particular inhibit the endogenous formation of carcinogenic N-nitroso compounds (NOC).

Moreover, it is well known that it is *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten*, 459 F.2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi*, 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

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Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is (703) 308-9432. The examiner can normally be reached on Monday through Friday from 7:15 am to 3:45 pm. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196 or the Supervisory Patent Examiner, Brenda Brumback whose telephone number is (703)3220.

Michele C. Flood
MCF **MICHELE FLOOD**
PATENT EXAMINER

March 24, 2003